REST/NRSF Knockdown Alters Survival, Lineage Differentiation and Signaling in Human Embryonic Stem Cells.

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Public Summary:
Dysregulation of a gene called REST that is active in nerve cells is thought to play a role in diverse diseases including epilepsy, cancer, Down's syndrome and Huntington's disease. Interestingly, we have found that changing REST activity in stem cell lines grown in culture leads to increased survival, not increased death as we suspected. Therefore we have uncovered a new role for REST in regulation of growth and early differentiation decisions in human embryonic stem cells grown in culture.

Scientific Abstract:
REST (RE1 silencing transcription factor), also known as NRSF (neuron-restrictive silencer factor), is a well-known transcriptional repressor of neural genes in non-neural tissues and stem cells. Dysregulation of REST activity is thought to play a role in diverse diseases including epilepsy, cancer, Down's syndrome and Huntington's disease. The role of REST/NRSF in control of human embryonic stem cell (hESC) fate has never been examined. To evaluate the role of REST in hESCs we developed an inducible REST knockdown system and examined both growth and differentiation over short and long term culture. Interestingly, we have found that altering REST levels in multiple hESC lines does not result in loss of self-renewal but instead leads to increased survival. During differentiation, REST knockdown resulted in increased MAPK/ERK and WNT signaling and increased expression of mesendoderm differentiation markers. Therefore we have uncovered a new role for REST in regulation of growth and early differentiation decisions in human embryonic stem cells.